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14. ABSTRACT

This report represents the fourth in a multi-year effort to improve outcomes in patients with traumatic brain injury (TBI) utilizing human and animal models. The first two years focused on infrastructure development, human use and basic science protocol development, staff acquisition, equipment purchase and database development. At the conclusion of Year 2, two human use protocols focusing on the inflammatory process following TBI and vital sign response to trauma had been instituted; development and testing of the Brain Resuscitation Registry (BRR) to provide structure and linkage capabilities for data collection and outcome reporting continued, and the animal sub-project underwent further development and re-formatting. Year 3 accomplishments included the ongoing enrollment of subjects in the human use protocols, development and implementation of 2 retrospective human use protocols, processing of specimens for the Cytokines sub-project, further development of the BRR and initiation of the basic science model including both small and large animal models of polytrauma. During Year 4 the existing human use protocols concluded data collection and neared finalization of data analysis, and a new protocol proposed. Progress continued in BRR development and reporting, and the animal sub-project neared completion. An additional no-cost extension was granted in August 2011, to allow for implementation of the final human use protocol and completion of data analysis.

15. SUBJECT TERMS
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INTRODUCTION

Traumatic Brain Injury (TBI) is the primary cause of trauma mortality in both civilian and military populations, a major source of long-term disability world-wide and a substantial independent cause of death in the U.S. The dominance of TBI in trauma epidemiology is due to our inability to treat primary central nervous system injury and the realization that the phenomenon of secondary brain injury (pathology at the metabolic, cellular, vascular and tissue levels) begins within seconds after the primary trauma and plays a profound role in the subsequent evolution of TBI. This multi-year effort to improve outcomes in TBI patients focused creation of an infrastructure necessary to associate elements of care for the TBI patient with specific and relevant outcomes, including establishment of a centralized Brain Resuscitation Registry (BRR) for data capture, deployment of equipment to capture continuous pre-hospital and in-hospital vital signs, and development of human use and basic science models.

Targeted efforts over the life of the project have included: a human use protocol to examine the contribution of inflammatory cytokines after TBI, retrospective protocols to examine the contribution of oxygen delivery and surgical timeframes to outcome from TBI, and both small and large animal sub-projects of controlled cortical impact. During the fourth year of the project, the existing human use protocols completed data collection and focused on analysis, and an additional human use protocol was identified and submitted for approvals. The animal models neared completion of development and the BRR continued development with a focus on reporting structure. A no-cost extension for the 5^{th} year of the project has been approved which will allow for implementation of the last human use protocol and finalization of data analysis for all sub-projects.

BODY

This is the annual report for Year 4 of a multi-year project. Table 1 below reflects the adjusted Project Milestones Timeline based on the actual funding award date of September 17, 2007. Start and finish date columns reflect target timelines while subsequent columns reflect actual task completion dates. Research progress is further summarized by the itemized sub-projects following the table.

Table 1: Timeline

Activity Name	Target Completion	Actual Completion
Vital Signs Sub-project		
**Complete matching of 2009 cases	16-Oct-2010	1-Oct-2010
**Development of real-time ICU Team View	16-Oct-2010	1-Oct-2010
**Development of TBI prediction methods and algorithms	16-Oct-2010	On-going
**Complete matching of 2010 cases	31-Mar-2011	01-Apr-2011
***Initial IRB approvals*	31-Jan-2008	02-Apr-2008
Cytokines Sub-project		
**Purchase of final assay kits	15-Apr-2011	01-Dec-2010
**Completion of assay processing	15-Apr-2011	04-Jan-2011
**Completion of data analysis	15-Feb-2012	
***Initial IRB approvals*	31-Jan-2008	29-Jul-2008
Brain Resuscitation Registry		
**Implementation of reporting process	15-Jan-2011	12-Jan-2011
**On-going refinement of reporting process	15-Oct-2011	
Retrospective Subprojects:		
TBI and Fracture Fixation *and*		
TBI, Oxygenation and Outcomes		
**Submission of abstracts	15-Jan-2011	04-Jan-2011
**Manuscript submission	1-Nov-2011	
***Initial IRB approvals*	15-Jan-2010	29-Mar-2010
Animal Subprojects		
**Continue development of rat polytrauma model	16-Oct-2010	01-May-2011
**Initiate rat protocol	15-Apr-2011	01-May-2011
**Completion of data collection	15-Sept-2011	On-going
**Initiate pig protocol	15-Jan-2011	01-April-2011
**Completion of data collection	15-Sept-2011	01-Oct-2011
**Obtain CCI device		10-Jan-2011
***IRB approvals*	01-Oct-2007	26-Feb-2008
TCD and BAM sub-project		
**Submission of protocol to IRB	16-Oct-2010	21-Feb-2011
**Submission of protocol to USAMRMC		05-April-2011
**Initiate protocol	30-Nov-2011	
***UMB IRB approval*		25-Mar-2011
***USAMRMC HRPO approval*		Pending

All human sub-projects have received IRB approval from the University of Maryland (UMB), IRB and the USAMRMC ORP, HRPO prior to implementation.

Sub-project 1: Vital Signs Data in Trauma Patients

This project was initially approved by UMB, IRB and USAMRMC ORP, HRPO upon continuing review on 2/21/08. This study was then re-assigned to the current project "Early Support of Intracranial Perfusion," on 2/26/08.

During Year 1 several amendments were made to the project including a waiver of informed consent. An amendment was also approved in October 2010 to increase subject enrollment to a total of 14,000 subjects. The most recent annual renewal for this protocol was submitted to UMB IRB in November and approved for continuation on 11/23/10. The continuing review report was submitted to USAMRMC ORP, HRPO on 12/21/10 and the acceptance memorandum received on 01/04/11.

Pre-hospital Vital Signs Data Collection (VSDC) system

During Year 1 emphasis was placed on the development of equipment and working with pre-hospital providers to expand capabilities to obtain pre-hospital vital signs (VS) data.

Year 2 focused on further development of pre-hospital VS analysis to allow auto cleaning of VS artifacts. Critical episodes of hypoxia (SpO2 <95%, <90% <75%, hypotension (SBP<90; <100 mmHg) and tachycardia (HR>120, >110,>100 bpm) were identified. Available pre-hospital cases were linked with trauma registry data for identification of outcomes such mortality, hospital /ICU length of stay, admit and discharge Glasgow Coma Scale (GCS) score, brain injury status (AIS-head), and ISS. In addition, review of medical records was completed to identify pre-hospital LSI (life saving interventions) and in-hospital emergency LSI during the first 4 hours.

During Year 3 a new LifePack system was introduced, and efforts focused on continued retrieval of these data and matching to potential subjects. Analysis was initiated based on vital sign waveform data collected in the pre-hospital management and in the first 60 minutes after admission to identify trends and prediction value of waveforms as compared to need for LSIs and outcomes.

During Year 4, approximately 250 pre-hospital VS case data were collected and matched with in-hospital Shock Trauma Center (STC) patient records. One hundred ninety –nine records were matched to STC patients, and for 175 (88%) of these cases, we were able to match them with in-patient and trauma registry outcomes data. The charts are currently being searched to obtain the pre-hospital run sheets and the timing and occurrence of LSIs. Once the data set has been validated then our existing outcome prediction software will be used to determine specificity and sensitivity (area under Receiver Operator Characteristic curve) of LSIs and outcome measurements.

Also during Year 4 a new proposal based on this work, *Continuous Non-Invasive Monitoring and the Development of Predictive Triage Indices for Outcome following Trauma* (U of MD PI Colin F Mackenzie) was funded by USAF (FA 8650-11-2-6D01).

In-hospital Vital Signs Data Collection (VSDC) system and Shock Trauma Physiological (STP) Registry

A limited system for VS data collection was in existence prior to the reassignment of this sub-project to the larger study. Therefore, emphasis in Year 1 was on system upgrades and expansion of VSDC capabilities. Expansion of the VSDC system from initial location in the Trauma

Resuscitation Unit (12 admission bays and 6 operating bays) to a total of 54 critical care bays/beds also occurred during Year 1. Data mining was then initiated and preliminary algorithms were developed.

During Year 2 the VSDC system was further developed. Due to the low return on consent forms from prospective subjects, an amendment for a waiver of consent was submitted and approved by both UMB and USAMRMC.

In Year 3, based on the gap analysis, our research findings demonstrated the following:

1) The dose of patient VS above or below a critical limit (SBP<90, ICP>30, CPP<50 etc) was determined to be a better predictor than the signal value alarm for predicting patient outcomes (mortality, length of stay and 3, 6, 12 month GOSE).
2) It is difficult to quickly identify the patterns of multi-VS critical episodes at a glance for the duration of 12/24 hours.
3) For real-time ICU management it is important to show a quick overview of the patient in the unit. To address the above challenges we developed a real-time ICU Team View (ICUTV) which providing at-a-glance views of the 12 bed ICU VS trends and critical episodes. The ICUTV was deployed at the STC Neuro Trauma ICU with a secured remote physician office access.

During Year 3, development of computer assisted auto patient physiological (VS) data identification software was also completed and introduced. This software facilitated the matching of 99.2% of the trauma admissions and the ultimate enrollment of 4,995 study subjects meeting study criteria. With improvements in the ability to accurately identify study subjects, a protocol modification is planned for the first quarter of Year 4 to increase the number of data sets available for analysis

By the end of Year 4, pre-hospital and admission VS data for more than 13,000 trauma patients admitted to the Shock Trauma Center (STC) in 2009 and 2010 were obtained from the trauma registry and analyzed using Receiver Operator Characteristic curves to predict the need for the LSI of a blood transfusion. Blood bank records identified those patients in this cohort who were alive on arrival, acutely hemorrhaging, and received blood and blood products within the first 24 hours. Findings indicated that pre-hospital and STC admission Shock Index (SI = heart rate/systolic blood pressure) had an 86% sensitivity and 81% specificity to predict blood and blood product use within 24 hours of STC admission (area under the Receiver Operator Characteristic curves of 0.72 and 0.78 respectively)**.** The importance of this finding is that a 20-30 minute 'heads up' in advance of casualty arrival obtained by automated SI decision- assist communicated from the field to the blood bank would allow for a full range of blood products to be thawed or otherwise processed to supply coagulation factors such as plasma and platelets in near equivalence with red cells.

Sub-project 2: Early Support of Intracranial Perfusion – Cytokines

The protocol was initially submitted to UMB IRB on 3/20/08 and after requested revisions the final protocol was approved by UMB, IRB on 7/28/08 and USAMRMC ORP, HRPO on 7/29/08. The most recent annual renewal for this protocol was submitted to UMB IRB on 2/01/11 and approved for continuation on 02/06/11. The continuing review report was submitted to USAMRMC ORP, HRPO on 03/09/11 and the acceptance memorandum received on 04/13/11.

Much of Year 1 focused on the standardization of policies and procedures for recruitment, specimen and data collection. The sub-project coordinator was assigned and identified research staff trained on recruitment and specimen/data collection procedures. Standardization of procedures for handling of collected specimens and specimen storage was completed during the fourth quarter of Year 1. Screening for this sub-project was opened on 8/20/08.

At the close of Year 2, 42 subjects had been enrolled in the study, with one screen-fail and one subject withdrawn. Eight of the 42 subjects expired due to their injuries. Preliminary analysis has focused on the first 30 cytokines subjects to study the relationship between the continuous patient VS (ICP, CPP, SBP, HR Variability and Pause Pressure Variability) and outcome (Mortality, hospital length of stay, surgical management, 3 Month and 6 Month GOSE). At the close of Year 2 sufficient assay materials required for processing the first 30 study subjects were ordered.

Enrollment of the 50 subject target was completed in January 2010 and follow-up thru 1 year post injury was completed on all available subjects in Year 4 (January 2011). At the conclusion of the follow-up period, 10 (20%) of the 50 subjects had expired due to their injuries. Of those remaining, 38 subjects completed their 3 month follow-up, 36 completed their 6 month follow-up and 31 completed a 12 month follow-up interview. One subject declined further follow-up upon contact at 6 months, and two subjects were unable to be reached after multiple attempts.

During Year 3, remaining assay materials were acquired, analysis of serum samples for the first half of the study cohort was completed and initial processing of all CSF samples completed. At the close of Year 4, assays for all serum and CSF samples had been processed and analysis on the complete grouping was near completion. Detailed analysis on all data components and their relationship to specific outcome measurements had been initiated, with final analysis expected early in the no-cost extension year.

Complete the Brain Resuscitation Registry network architecture

During Year 1, secure web-based trauma registry containing clinical patient information for trauma patients was established. Year 2 focused on the continuing development of the network architecture. Links were established to automate the extraction of patient data needed to profile, enroll, manage and analyze current study populations. Study protocols were centralized and automated allowing for the establishment of communication between studies. Screens were added to the registry for current trauma patients to accomodate selection and clinical data management. The Cytokines sub-project served as the test study for these processes and for the training of research staff.

Year 3 progress included the installation of a dedicated server which, along with the purchase of dedicated screening tablets, allowed the implementation of a fully active automated screening process. Screening of all TRU Patients is now tracked through the system. Addition of a minimum required data feature ensures that key trauma data points are captured before the system will permit a patient to be closed out even if he/she is not suited for any study.
Adjustments to the rules module (and its interface) were finalized so that it may accurately filter the required include/exclude criteria for the studies currently in the system.
The system restricts users on a study-by-study basis and can permit view only roles or other access restrictions based on the user's job responsibilities and study privileges. Reporting has

continued to be developed. There are now real time screening statistics on each study that provide information on how many relevant patients were screened and the breakdown of why candidates were ineligible for a particular study.

Latest enhancements during Year 4 include security and workflow processes enhanced to allow a secondary screening phase if a study requires it. This permits study coordinators to distribute more intensive data collection responsibilities to specific users without holding up the patient in studies for which they have already been excluded. A dedicated interface is being installed between the main clinical information and the BRR. This will allow more autonomy and stability as it will not be dependent on ancillary systems for ADT data.

The outcomes survey process is now fully up and running allowing bi-weekly imports of completed outcome surveys. These surveys are administered on ScanTron forms that are then imported into the BRR and linked to the patients' initial screening and treatment data. The process has been enhanced to merge with the scheduling system so that the survey forms are pre-printed with the patient information prefilled out, thus making the visit matching process much more accurate and allowing for better auditing of staff compliance. Additionally, instant evaluation of the outcomes forms and coordination between the Shock Trauma clinic and rehab clinics is helping to aid in providing patients with immediate referrals for follow-up services.

A reporting database module is being developed that joins the three systems of the trauma registry, the Brain Resuscitation Server and the outcomes data. This will allow adhoc querying and data mining of anonymous case histories by researchers. It will also allow access of qualified users to full queries within the scope of their study protocols and regulations.
An intranet Wiki server has been set up allowing documentation of the Brain Resuscitation System for both technical and user personnel which permits easy online access to all help manuals.

We are continuing to evolve relationships with the state's first responder agency in hopes of taking advantage of their enhancements to their field data collection systems. These new systems will allow better and faster sharing of pre-hospital data from the trauma scene.

Retrospective Sub-projects

Two new retrospective sub-projects were initiated in Year 3, in preparation for prospective studies. Both were approved by UMB IRB as exempt protocols on 02/24/10 and approved as exempt by USAMRMC on 03/29/10

Traumatic Brain Injury and Fracture Fixation

Traumatic Brain Injury, Oxygenation and Outcomes

<u>Traumatic Brain Injury and Fracture Fixation</u>

The records for 167 consecutive TBI subjects with femoral shaft fractures between 06/2002 and 06/2009 were reviewed and analysis was completed. All patients with a head AIS > 2 who survived at least 12 hours beyond admission were included in the study.

One abstract based on these analyses has been presented and a manuscript is undergoing final revisions for submission.

Traumatic Brain Injury, Oxygenation and Outcomes

Data for 1660 consecutive TBI subjects admitted between 06/2002 and 06/2009 were reviewed to identify predictors of outcome based on FiO2 delivery and analysis was completed.

Two abstracts have been submitted (1 already presented) based on this work, and a manuscript was recently submitted for publication

Sub-project 3: Animal Model of Brain Injury

The animal use protocol described in the initial statement of work was approved by the UMB IACUC on 9/21/07. It was subsequently submitted to the USAMRMC Animal Care and Use Review Office (ACURO) on 11/27/07. In response to the review by the USAMRMC ACURO, a revised protocol was submitted on 2/25/08 and approved by USAMRMC ACURO on 2/26/08.

During the course of Year 2, the model was changed to a large and small animal polytrauma model of contusional brain injury (controlled cortical impact) plus hemorrhagic shock. This change was necessary due to challenges in finding a vendor for the device necessary for conducting the penetrating brain injury paradigm with large animals, and feedback from the review of the last annual report that a large animal model of polytrauma caused by TBI plus hemorrhagic shock would be more clinically translational than that of a rodent model. A revised SOW was developed using a combination of both controlled cortical impact plus hemorrhagic shock with adult male Sprague Dawley rats and with adult male Hanford miniature swine (Sinclair Bio-resources).

In Year 3, the pig CCI model was finalized and approvals received by both UMSOM and ACURO. Development, equipment procurement and initiation of the two planned small and large animal model protocols proved more challenging than originally identified. Over Year 3 the original goal of developing a rat polytrauma model consisting of controlled cortical impact (CCI)-induced contusional brain injury plus hemorrhagic shock was reached. As expected the combination of hemorrhagic shock plus CCI results in death to cells in the cerebral cortex (cortical lesion volume) that is significantly greater than that obtained with CCI alone. One consequence of hemorrhagic shock is a systemic inflammatory reaction that can result in multiple organ failure. While the degree of hypotension induced in our model is not sufficient to produce multiple organ failure, it is sufficient to induce systemic inflammation. We hypothesized that this reaction is responsible for the greater cortical lesion volume observed with the polytrauma model compared to that with CCI alone. At the end of Year 3 the CCI device for use in both the large and small animal models was purchased.

Rat model

Over 60 rat experiments with the device have been completed. The last 10 performed in an identical manner with a 1.5 mm depth of cortical impact, demonstrated consistent cerebral infarct volumes. All of these animals survived. When this degree of brain injury was combined with hemorrhagic shock, 4 out of 5 animals died within 24 hours after injury. We have now reduced the depth of impact to 1.25 mm and all of the last 4 animals survived. We plan on conducting another 6 experiments before starting the randomized and blinded study testing for sulforaphane to reduce brain infarct volume in these animals that undergo TBI plus hemorrhagic shock.

Mini-pig model

During Year 4 efforts tested the above hypothesis through a series of directed experiments. During this period, we sought to establish a dose-response relationship between CCI impact depth and cortical lesion volume, using a large animal model consisting of mini-pigs. Progress on this aim has been delayed by the difficulty in finding a company that would supply an appropriate CCI device and stereotaxic head-holder for pigs. The device was ordered late in Year 3 and was received during Year 4.

We have successfully developed the skills required to independently provide sedation, establish a peripheral venous access point, properly place an endotracheal tube, and induce and manage the appropriate level of anesthesia to the animal throughout all surgical procedures. In addition, we have since learned how to control and maintain blood gases within physiologic ranges by adjusting mechanical ventilatory parameters, perform the craniotomy such that the desired cortical area receives a given impact depth, and collect brain in a manner permitting histopathological analyses. The development of this model has been slow, based on learning neurosurgical techniques specific for pigs. Specifically, since a pig's skull is exceptionally thick, different types of drilling equipment were used to optimize the bore hole necessary for access of the CCI device to the cortical surface without causing ruptured dura and non-survivable injury.

Methods: Ten male miniature Hanford swine weighing 38-45 kg were fasted 8 hours prior to surgical preparation. Animals were initially sedated by intramuscular injection of a mixture of Telazol (4.4 mg/kg) / Xylazine (2.2 mg/kg). Pigs were subsequently anesthetized with a mixture of Propofol (4 mg/kg) and Fentanyl (5 mcg/kg/hr), intubated and subjected to mechanical ventilation (10 bpm, 10cc/kg) for the duration of all surgical procedures. Left femoral and arterial catheters were placed for blood pressure monitoring and drug delivery. The pigs head was fitted into a large animal stereotactic frame to ensure rigid fixation of the skull thus preventing movement during controlled cortical impact. The skull was exposed and a 7/8" craniectomy was made on the left side of the skull, 1mm from midline and 1mm from Lambdoid suture, to expose the dura for impact. Cortical injury depth was set at 7mm, with duration of 50 msec and delivered at 5.0 m/sec with a 15 mm impactor tip. Following impact, the scalp incision was closed and the animal maintained under critical care for an additional 4 hours. At this time, the animal was transcardially perfused with 4% paraformaldehyde and the brain collected for gross anatomical and histopathological studies.

Results: We have successfully been able to alter the degree of injury delivered with the new cortical impact device. While our initial impact parameters were based on Dr Panter's published data, experiments performed in our laboratory have demonstrated that a cortical impact of 11 mm depth delivered at 5.0 m/s by our newly constructed CCI device results in a ruptured dura with herniated brain matter. In addition to widely evident subdural hemorrhaging, a depth of 11 mm results in widespread subarachnoid hemorrhaging on both the injured as well as the uninjured cerebral hemispheres (frontal, parietal, temporal and occipital) and cerebellum.

Our most recent experiment tested an impact depth of 7 mm delivered at 5.0 m/s and resulted in a moderate injury where the dura was left intact with no herniation of brain matter. Although there was subdural hemorrhaging localized to the impact site on the ipsilateral hemisphere, there was no evidence of subdural hemorrhaging on the contralateral hemisphere and minimal bilateral subarachnoid hemorrhaging was contained to the cortical temporal and occipital lobes.

Activation of inflammatory processes and neuronal degeneration as evidenced by FJB positive cells, condensed chromatin, loss of NeuN immunoreactivity and axonal beading and occur within

4 hours following 7mm controlled cortical impact in the cavity penumbra as well as in the ipsilateral hippocampus.

Work over the no-cost extension year will test the hypothesis that injection of polytrauma rats with sulforaphane will significantly reduce the brain infarct volume. Our measurements will also test the hypothesis that sulforaphane increases levels of antioxidant proteins, e.g., NADPH/CoQ oxidoreductase, anti-inflammatory proteins, e.g., heme oxygenase, and decrease markers of oxidative stress, e.g., DNA oxidation, in the brains of animals that undergo CCI plus hemorrhagic shock. Positive results will form the basis of more translational experiments performed with large animals, e.g., pigs, that could then lead to clinical trials testing for neuroprotection by sulforaphane for polytrauma TBI victims.

New sub-project: Transcranial Doppler and Brain Acoustic Monitoring

At the end of Year 3, a protocol to evaluate two non-invasive tools for assessment of cerebral perfusion and vasospasm in patients with severe TBI was developed. This protocol will use both Transcranial Doppler (TCD) screening and the Brain Acoustic Monitor (BAM) to study the incidence of vasospasm in patients with severe TBI. Using well-established criteria for vasospasm detected with TCD, the BAM device data will be analyzed to determine the ability to apply this non-invasive bedside tool to improve diagnostic capabilities in patients with severe TBI. Forty patients with severe TBI will be enrolled in this pilot study. Daily TCDs and BAMs will be obtained for 7 days following injury. Dr Kevin Sheth will be joining the research team as a co-investigator for this study. The protocol was initially approved by UMB IRB in March 2011, and requested USAMRMC HRPO modifications approved by UMB IRB in June 2011. USAMRMC approval is currently pending additional requests from UMB IRB. Data collection and analysis for this sub-project was one of the key reasons for the additional no-cost extension request.

KEY RESEARCH ACCOMPLISHMENTS

Sub-project 1: Vital Signs Data in Trauma Patients

At the close of Year 1

- Enhanced the pre-flight patient Vital Signs data collection network
- Developed and expanded the in-trauma center VS data collection network to cover all critical care bays (TRU, OR, ICU)
- Developed and deployed a total pre and in-hospital VS data collection network
- Developed a basic VS data mining system to collect, process, and predict patient outcomes
- Established a road map for innovative prediction algorithm development

At the close of Year 2

- Completed the hospital/center based real-time patient physiological data collection network (covers all 90 trauma center beds)
- Developed a basic real time Shock Trauma Physiological (STP) Registry.

Key research findings include:

  - Continuous pre-hospital VS reviewed by 3 Subject Matter Experts (SME) identified more critical episodes (up to 300%) than Trauma Registry (TR).N=177
  - SME identified critical episodes (HR>120 bpm, SpO2<90, SBP<90mmHg) predicted outcome (mortality, length of stay, discharge GCS) better than TR. N=177.
  - Continuous pre-hospital VS better predicted emergency LSIs than TR (N=177)
  - EMS pre-hospital protocols may be monitored remotely in pre hospital care of TBI. (N=64)

At the close of Year 3

- Development of a computer assisted auto patient physiological (VS) data identification software, facilitating the successful matching of the 2008-2009 STC admission VS data for patients fitting enrollment criteria
- Continued development and refinement of continuous VS based prediction models
- Development of real-time ICU Team View (ICUTV), providing at-a-glance views of the 12 bed Neuro ICU VS trends

At the close of Year 3, a transition plan for the VS project was initiated. Information on the methods and strategies proposed to move the VS product to the next phase of development includes submission of a funding request to USAF to examine the Pulse Oximeter signal in more detail than is currently possible with infrastructure and equipment available under the current funding. In brief, the project seeks to identify, test and validate accuracy of algorithms, models and sensors to predict adverse events and the necessity for actionable therapeutic interventions including: hypoxemia, hemorrhagic shock, need for blood transfusion, chest tube insertion, airway management and other LSIs, and abdominal surgery to control hemorrhage.

At the close of Year 4

- Completion of case matching for 2010
- The project, titled "Continuous non-invasive monitoring and the development of predictive triage indices for outcome following trauma," was funded by USAF (FA 8650-11-2-6D01); UM PI: Colin mackenzie, USAF PI: Joseph J DuBose
- The project, titled "Traumatic Injury and Medical Evacuation – Patient Outcomes (TIME-PO), was funded by USAF (FA8650-11-2-6D03); USAF PI: David Power

- For the project, titled "The Vitals Signs 'Genome Project'- Computational gene mapping to analyze continuous automated real-time vital signs monitoring data" a funding response is imminent; UM PI: Deborah Stein
- The project, titled "Predicting casualty blood product needs using pre-hospital vital signs" has been submitted to USAFMSA

Sub-project 2: Early Support of Intracranial Perfusion – Cytokines

At the close of Year 2

- Recruitment of 42 study subjects

30 cytokines cases were used to study the relationship between the continuous patient VS (ICP, CPP, SBP, HR Variability and Pause Pressure Variability) and TBI patient outcome (Mortality, hospital length of stay, time of craniotomy, 3 Month, 6 Month and 12 month GOSE). The findings are

  - ICU ICP>20, 30 CPP<50<60 predicts patient outcome better than patient charts VS.
  - Combined ICP>20 and CPP<60 episodes predict outcome better than individual ICP and CPP.
  - Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI.
  - The "Brain Trauma Index": Dynamic 3-D scoring in the assessment of TBI
  - Computerized patient vital signs charting method enhances real-time record keeping in ICU
  - Heart rate variability is associated with intractable intracranial hypertension and cerebral hypoperfusion

At the close of Year 3

- Recruitment of targeted 50 subjects
- Preliminary processing of serum and CSF samples for all subjects
- Analysis of all samples and correlation to clinical markers of TBI severity
- Determination of serum and CSF biomarkers that predict worsening of cerebral hypoperfusion, intracranial hypertension, and cerebral hypoxia.

At the close of Year 4

- Data collection and longitudinal follow-up was completed
- Processing of serum and CSF samples was completed
- Detailed analysis of all data points is nearing completion

Sub-projects – Retrospective

TBI and Fracture Fixation

At the close of year 3, preliminary analysis completed, key findings include:

- Early femur fracture fixation in TBI subjects correlates with significantly reduced hospital and ICU length of stay
- Early definitive fracture stabilization has no detrimental effect on mortality and discharge GCS
- 1 abstract has been presented and 1 manuscript is nearing final preparation for submission

TBI, Oxygenation and Outcomes

At the close of year 3, preliminary analysis nearing completion, early key findings include:

- Hyperoxemia within the first 24 hours of hospitalization increases mortality and worsens short-term functional outcomes in TBI subjects.
- Poor outcomes may be predicted by hypoxia within the first 24 hours of admission

At the close of Year 4,

- 2 abstracts have been accepted (1 presented) and 1 manuscript is nearing final preparation for submission

Sub-project 3: Animal Model of Brain Injury

At the close of Year 2

- A rat polytrauma model consisting of controlled cortical impact traumatic brain injury plus hemorrhagic shock had been successfully developed.
- Preliminary experiments performed with human cerebrospinal fluid samples indicate that they can be used in a new and novel assay that detects toxicity of these samples on culture cell lines, using cellular respiration and glycolysis as outcome measures

At the close of Year 3

- Rat model for CCI plus hemorrhagic shock was finalized
- CCI device for both rat and mini-pig models purchased

At the close of Year 4

- Initiation of rat CCI model
- Initiation of mini-pig CCI model

REPORTABLE OUTCOMES

a) Presentations:

5th Annual Innovations in the Surgical Environment Conference, June, 2008

Lesson learned: developing in-fight patient vital-signs data collection network
Hu P, Handley C, Sen A, Seebode S, Conway A, Gens R, Kramer B, Jordan S, Webb R, Defouw G, Davies P, Ho D, Xiao Y, Mackenzie C, and Trauma Vital Signs Investigator and Associates (TVSI,TVSRA) Group

Can pre-hospital patient VS predict injury and intervention?
Hu P, Mackenzie C, Dutton R, Sen A, Floccare D, Bochicchio G, Xiao Y, Spearman J, Scalea T.

Challenges in developing real-time patient vital sign data collection network for trauma care. Hu PF, Mackenzie CF, Dutton R, Bochicchio GV, Bochicchio K, Xiao Y, Spearman J, Scalea T.

American Telemedicine Association Annual meeting, April, 2008

Challenges in developing real-time in-flight patient vital-signs data collection system.
Hu P, Handley C, Seebode S, Conway A, Gens R, Mackenzie C, Ho D, Defouw G, Davies P, Floccare D.

Real-time Patient Vital Sign Data Collection Network for Trauma Care.
Hu P, Mackenzie C, Dutton R, Bochicchio G, Bochicchio K, Xiao Y, Spearman J, Scalea T.

American Society of Anesthesiologists Annual Conference, October, 2008

Continuous prehospital vital signs record identifies increased abnormalities/predicts interventions. Sen A, Hu P, Mackenzie C, Jordan S, Dutton R.

Correlation between ECG heart rate and pulse oximeter heart rate in prehospital aeromedical trauma transfer. Sen A, Hu P, Dutton RP, Mackenzie CF, Alexander M, Xiao Y.

American Medical Informatics Association Annual Symposium November, 2008

Automatic pre-Hospital vital signs waveform and trend data capture fills quality management, triage and outcome prediction gaps. Mackenzie C, Hu P, Sen A, Dutton R, Seebode S, Floccare D, Scalea T.

Statewide real-time in-flight trauma patient vital signs collection system. Hu P, Mackenzie C, Dutton R, Sen A, Xiao Y, Handley C, Ho D, Scalea T.

American Telemedicine Association Conference, April, 2009

Automated vital-sign recording identifies more critical episodes than chart abstraction. Hu P, Sen Y, Mackenzie C, Xiao Y, Jordan S, Dutton R, Scalea T, and Trauma Vital Signs Research Group (TVSG)

Can EMS protocols be monitored remotely in pre hospital care of traumatic brain injury (TBI)? Mackenzie C, Hu P, Sen A, Xiao Y, Jordan S, Dutton R, Scalea T.

16th World Congress of Disaster and Emergency Medicine, May, 2009

Continuous vital signs acquisition improves prehospital trauma triage. Sen A, Hu P, Mackenzie C, Jordan S, Xiao Y, Dutton R, Scalea T

In-flight vital signs blackbox for trauma care. Hu P, Mackenzie C, Dutton R, Sen Y, Xiao Y, Floccare D, Scalea T.

Video technologies in emergency health research in assessing quality of care: a study of trauma resuscitation milestones. Sen A, Hu P, Mackenzie C, Xiao Y, Dutton R.

American Association for the Surgery of Trauma AAST 2009 Annual Meeting, October, 2009

Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI. Kahraman S, Hu P, Xiao Y, Dutton R, Aarabi B, Stein D, Scalea T.

American Society of Anesthesiologists ASA2009 Annual Meeting October, 2009

Real-time patient vital signs data registry for trauma patient care. Dutton R, Hu P, Xiao Y, Yeatts D, Mackenzie C.

High resolution ICP and CPP data better predict outcome of severe TBI. Dutton R, Kahraman S, Hu P, Xiao Y, Scalea T.

American Medical Informatics Association AMIA 2009 Annual Meeting November, 2009

CPP/ICP dose index: Dynamic 3-D scoring in the assessment of TBI. Kahraman S, Hu P, Xiao Y, Dutton R, Stein D, Scalea T.

Computerized patient vital signs charting method enhances real-time record keeping in ICU. Hu P, Akozer S, Lindell A, Liu K, Mitrou M, Gettings L, Stein D, Xiao Y.

Is there added value in continuous vital signs and video collection linked to trauma patient outcomes? Hu P, Mackenzie CF, Xiao Y, Seebode D, Wong M, Murdock K, Dutton R.

Society for Critical Care Medicine's 39th Critical Care Congress January, 2010

Heart rate variation is associated with intractable intracranial hypertension and cerebral hypoperfusion. Kahraman S, Dutton R, Hu P, Stansbury L, Xiao Y, Stein D, Scalea T .

Critical care monitoring in the field: Pre-hospital continuous vital signs acquisition identifies best predictors of life-saving interventions in trauma patients. Sen A, Hu P, Mackenzie C, Dutton R, Jordan S, Xiao Y, Scalea T.

Cerebrospinal fluid levels of inflammatory mediators: association with outcome following severe traumatic brain injury. Stein DM, Murdock KR, Menaker J, Bochicchio GV, Dutton RP, Aarabi B, Scalea TM.

Eastern Association for the Surgery of Trauma (EAST) 23rd Annual Scientific Assembly, January 2010

CSF levels of NSE and S100B in patients with severe TBI: correlation with clinical measures. Stein DM, Murdock KR, Kufera JA, Menaker J, Bochicchio GV, Dutton RP, Aarabi B, Scalea TM.

6th Innovations in the Surgical Environment Conference March, 2010

Trauma center wide real-time patient vital signs data registry (VSDR) for improvement of patient safety. Hu P, Stein D, Xiao Y, Dutton R, Kahraman S, Yeatts D, Grissom T, Mackenzie C, Scalea T.

International Society for Magnetic Resonance in Medicine, May, 2010

Early diffusion changes following controlled cortical impact injury on a rat model. Zhuo J, Xu S, Racz J, Fiskum G, Gullapalli R.

Early metabolic changes following focal traumatic brain injury in rats measured using 1H MRS. Xu S, Roys S, Racz J, Shi D, Zhou J, Gullapalli R, Fiskum G.

2010 American Telemedicine Association Annual International Meeting May, 2010

High frequency ICU perfusion pressure critical episodes predicts TBI patient outcomes. Hu P, Akozer S, Dutton R, Stein D, Murdock K, Xiao Y, Scalea T.

Association of University Anesthesiologists, Annual Meeting, May 2010

New uses of vital signs signals during resuscitation to triage, assess provider performance and predict outcomes.
Mackenzie CF, Hu PF, Ayan S, Woodford M, Floccare D, Scalea T.

NNS 2010: 28th Annual National Neurotrauma Symposium, June 2010

Early hypotension redefined in patients with severe TBI. Stein, DN, Brenner M, Sheth K, Hu P, Aarabi B, Scalea T.

Early fracture fixation improves select outcomes in TBI patients.
Brenner M, Stein DM, Hu P, Scalea T

8th Annual Neurocritical Care Society Meeting, September 2010

Association of CSF biomarkers and secondary insults following severe traumatic brain injury. Stein D, Kufera J, Lindell A, Murdock KR, Menaker J, Bochicchio GV, Aarabi B, Scalea TM.

Depth and duration of secondary insults predicts outcome in patients with severe traumatic brain injury. Stein D, Hu P, Kahraman S, Brenner M, Sheth K, Aarabi B, Scalea TM

American Association for the Surgery of Trauma (AAST 2010) Annual Meeting, September 2010

Relationship of serum biomarkers to depth and duration of secondary insults following severe TBI.
Stein D, Lindell A, Murdock K, Menaker J, Keledjian K, Bochicchio G, Scalea T.

Dynamic three-dimensional scoring of cerebral perfusion pressure and intracranial pressure provides a Brain Trauma Index that predicts outcome in patients with severe TBI.
Kahraman S, Dutton R, Hu P, Stansbury L, Hess J, Xiao Y, Stein D, Scalea T.

American Society of Anesthesiologists Annual Scientific Meeting. October 2010

Continuously recorded SPO2 outperforms SPO2 from trauma registry in prediction of mortality. Woodford M, Mackenzie CF, Hu P, Dutton R, Scalea T.

Failure to achieve normothermia is not associated with worsened outcomes in brain injury patients. Grissom T, Hu P, Dubose J, Dutton R, Stein D.

American Medical Informatics Association Annual Symposium, November, 2010

Using vital signs network to improve patient safety: How many alarms are too many?
Hu P, Mackenzie C, Stein D, Chang W, Seebode S, Binder M, Kramer ME, Xiao Y.

Eastern Association for the Surgery of Trauma (EAST) 24th Annual Scientific Assembly, January, 2011

Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome following severe traumatic brain injury. Stein D, Hu PF, Brenner M, Sheth K, Aarabi B, Scalea TM.

Western Association for the Surgery of Trauma (WEST) 2011 Annual Scientific Assembly

Traditional Systolic Blood Pressure Targets Underestimate Hypotension-induced Secondary Brain Injury. Brenner M, Stein DM, Hu PF, Aarabi B, Sheth K, Scalea TM

American Telemedicine Association Annual Meeting 2011

Pre-hospital hypoxemia and tachycardia trends better predict patient mortality than Trauma Registry values Hu P, Woodford M, Mackenzie CF, Dutton R, Seebode S, Liu K, Scalea T.

Brief Episodes of Abnormal Shock Index Predicts Mortality in Severe Traumatic Brain Injury. Hu P, Stein DM, Stansbury L, Brenner M, Kufera J, Xiong W, Jiao X, Scalea T.

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Real- time decision support during trauma patient resuscitation. Mackenzie CF, Hu PF, Stein D, DuBose J, Grissom T.

National Neurotrauma Society Symposium July 2011

Use of serum biomarkers to predict cerebral hypoperfusion following severe traumatic brain injury. Stein DM, Lindell A, Murdock K, Kufera J, Menaker J, Bochicchio G, Aarabi B, Scalea T.

b) Accepted for presentation:

Pacific Coast Surgical Association, February 2012

Early hyperoxia worsens outcomes after traumatic brain injury (TBI). Brenner M, Stein D, Hu P, Kufera J, Woodford M, Scalea T.

c) Publications (Journal or Proceedings):

Proceedings – abstracts and full length articles

Mackenzie CF, Hu P, Sen A, Dutton R, Seebode S, Floccare D, Scalea T. **Automatic pre-hospital vital signs waveform and trend data capture fills quality management, triage and outcome prediction gaps.** AMIA Annu Symp Proc. Nov 6:318-22, 2008

Hu PF, Handley C, Seebode S, Conway A, Gens Y, Mackenzie C, Ho D, Defouw G, Davies P, Floccare D. **Challenges in Developing Real-Time In-Flight Patient Vital-Signs Data Collection System**. Telemedicine and e-Health. 14(1)105, 2008

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Hu P, Handley C, Sen A, Seebode S, Conway A, Gens R, Kramer B, Jordan S, Webb R, Defouw G, Davies P, Ho D, Xiao Y, Mackenzie C **Lesson Learned: Developing In-Flight Patient Vital-Signs Data Collection Network** Proceedings of 5th Annual Innovations in the Surgical Environment Conference, 2008

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Hu PF, Mackenzie C, Dutton RP, Sen A, Floccare D, Bochicchio G, Xiao Y, Spearman J, Scalea T. **Can Pre-Hospital Patient VS Predict Injury and Intervention?** Proceedings of 5th Annual Innovations in the Surgical Environment Conference, 2008

Sen A, Hu P, Mackenzie C, Jordan S, Dutton R. **Continuous Prehospital Vital Signs Record Identifies Increased Abnormalities/Predicts Interventions**. Proceedings of the American Anesthesiologists Annual Conference A1637. 2008

Sen A, Hu P, Mackenzie C, Jordan S, Xiao Y, Dutton R, Scalea T. **Continuous Vital Signs acquisition improves prehospital trauma triage.** Prehospital and Disaster Medicine 24(2):s139. 2009

Mackenzie C, Hu P, Sen A, Xiao Y, Jordan S, Dutton R, Scalea T,.**Can EMS Protocols be monitored remotely in pre hospital care of Traumatic Brain Injury (TBI)?** Telemedicine and e-Health, 15(1) S-72. 2009

Kahraman S, Hu P, Xiao Y, Dutton R, Aarabi B, Stein D, Scalea T. **Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI** . Proceedings of American Association for the Surgery of Trauma (AAST) Annual Conference, 2009

Hu P, Sen A, Mackenzie C, Xiao Y, Jordan S, Dutton R, Scalea T, and Trauma Vital Signs Research Group (TVSG). **Automated vital-sign recording identifies more critical episodes than chart abstraction.** Telemedicine and e-Health, 15(1), S-73. 2009

Dutton R, Kahraman S, Hu P, Xiao Y, Scalea T. **High resolution ICP and CPP data better predict outcome of severe TBI**. Proceedings of the American Society of Anesthesiologists Annual Conference A451154, 2009

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Hu P, Mackenzie C, Xiao Y, Seebode S, Wong M, Murdock K, Dutton R. **Is there Added Value in Continuous Vital Signs and Video Collection linked to Trauma Patient Outcomes?** Proceedings of the American Medical Informatics Association AMIA-0094-A2009, 2009

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Hu P, Akozer S, Dutton R, Stein D, Murdock K, Xiao Y, Scalea T. **High frequency ICU perfusion pressure critical episodes predicts TBI patient outcomes** Proceedings of the American Telemedicine Association Annual Conference, May 2010

Stein DM, Hu P, Kahraman S, Brenner M, Sheth K, Aarabi B, Scalea TM. **Depth and Duration of Secondary Insults Predicts Outcome in Patients with Severe Traumatic Brain Injury.** Proceedings of Neurocritical Care Society Meeting, September 2010

Stein DM, Brenner M, Sheth K, Hu PF, Aarabi B, Scalea TM. **Early hypotension redefined in the patients with severe traumatic brain injury.** Proceedings of 28th Annual National Neurotrauma Society Symposium June 14-17, 2010

Brenner M, Stein D, Hu P, Kufera J, Scalea T. **Early Fracture Fixation Improves Select Outcomes in Traumatic Brain Injury Patients** Proceedings of 28th Annual National Neurotrauma Society Symposium June 14-17, 2010

Grissom T, Hu P, Dubose J, Dutton R, Stein D**. Failure to achieve normothermia is not associated with worsened outcomes in brain injury patients.** Proceedings of American Society of Anesthesiologists Annual Scientific Meeting, 2010

Hu P, Mackenzie C, Stein D, Chang W, Seebode S, Binder M, Kramer ME, Xiao Y. **Using vital signs network to improve patient safety: How many alarms are too many?** Proceedings of American Medical Informatics Association Annual Symposium, 2010

Kahraman S, Dutton R, Hu P, Stansbury L, XiaoY, Stein D, Hess J, Scalea T. **Cerebral perfusion pressure/intracranial pressure dose index: Dynamic 3-D scoring in the assessment of Traumatic Brain Injury** Proceedings of American Association for the Surgery of Trauma (AAST) Annual Conference. September 2010

Stein D, Hu PF, Brenner M, Sheth K, Aarabi B, Scalea TM. **Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome following severe traumatic brain injury.** Proceedings of Eastern Association for the Surgery of Trauma (EAST) 24th Annual Scientific Assembly, 2011

Brenner M, Stein DM, Hu PF, Aarabi B, Sheth K, Scalea TM. **Traditional Systolic Blood Pressure Targets Underestimate Hypotension-induced Secondary Brain Injury**. *Proceedings of* Western Association for the Surgery of Trauma (WEST) 2011 Annual Scientific Assembly

M Brenner, D Stein, P Hu, J Kufera, M Wooford, T Scalea **Too much of a good thing? Early hyperoxemia worsens outcomes in TBI patients** Proceedings of Western Association for the Surgery of Trauma (WEST) 2011 Annual Scientific Assembly

Hu P, Woodford M, Mackenzie C, Dutton R, Seebode S, Liu K, Scalea T. **Pre-hospital hypoxemia and tachycardia trends better predict patient mortality than Trauma Registry values** Proceedings of American Telemedicine Association Annual Meeting ATA 2011

Hu P, Stein D, Stansbury L, Brenner M, Kufera J, Xiong W, Jiao X, Scalea T. **Brief Episodes of Abnormal Shock Index Predicts Mortality in Severe Traumatic Brain Injury.** Proceedings of American Telemedicine Association Annual Meeting ATA 2011

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Stein D, Stansbury L, Hu P, Chang, Scalea T, **Computational Gene-Mapping to Analyze Continuous Automated Physiologic Monitoring data in Neuro-trauma Intensive Care** Proceedings of Eastern Association for the Surgery of Trauma (EAST)2011 .

Journals

Kahraman S, Dutton RP, Hu P, Xiao Y, Aarabi B, Stein DM, Scalea TM **Automated Measurement of "Pressure Times Time Dose" of Intracranial Hypertension Best Predicts Outcome After Severe Traumatic Brain Injury.** Journal of Trauma 2010; 69(1):110-118.

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d) Accepted for publication

Brenner M, Stein DM, Hu PF, Aarabi B, Sheth K, Scalea TM. **Traditional systolic blood pressure targets underestimate hypotension-induced secondary brain injury.** J Trauma.

CONCLUSIONS

At the conclusion of Year 4 significant progress has been made toward meeting overall project milestones. The infrastructure of staff, technology and data management to support the completion of sub-projects and long-term assessment of TBI patients had been created. The robust Brain Resuscitation Registry (BRR) needed to accomplish the goals of this multi-year project has been implemented and continues to undergo refinement especially in terms of reporting. Recruitment and data collection for the Vital Signs human sub-projects is completed and data analysis and prediction model development on-going. Sub-project 2, Cytokines has completed subject recruitment and follow-up, specimen processing and initial data analysis. It is anticipated that final data analysis will be complete early in the no-cost extension (Year 5). Both animal sub-projects have been initiated, and animal experiments will continue during the no-cost extension year. Two retrospective human sub-projects have been completed and manuscripts detailing the results are nearing completion. The protocol for the final new human use sub-project has been submitted, and is awaiting approval from the appropriate IRB / HRPO authorities.

REFERENCES

No new literature searches were undertaken in Year 4.

APPENDICES

Abstracts Accepted or Presented since last Annual Report

Continuously Recorded SPO2 Outperforms SPO2 from Trauma Registry in Prediction of Mortality

Introduction: Early prediction of outcomes and interventions in trauma patients is difficult in the field. Pre-hospital healthcare providers rely on intermittent measurement of vital signs and physical assessment to predict patient management needs. There is correlation between manually recorded physiological data and prediction of interventions, but it is consistent with the current problem of over triage.[1] Currently trauma injury scores (ISS, TRISS, RTS) accurately predict patient outcomes, although that data is not available until the patient has been admitted and fully evaluated.[2] We hypothesize that continuously recorded vital signs, specifically oxygen saturation (SPO2), available in real time in the pre-hospital setting can predict patient mortality early and accurately.

Methods: This is an IRB approved retrospective analysis of vital signs data collected continuously from 177 trauma patients admitted to University of Maryland Shock Trauma Center (STC) between May 2007 and February 2008. All patients were transported via helicopters equipped with Vital Sign Data Recorders (VSDR). Pre-hospital continuous SPO2 from VSDR and the manual recorded SPO2 from the trauma registry (TR) were compared against mortality. The VSDR and TR vital signs were analyzed using Receiver Operating Characteristic (ROC) curves to assess the ability of each method to predict mortality. Clinical cutoff values (i.e. SPO2 <90%) and durations (5, 10, 15 minutes) in the VSDR group were analyzed in the same fashion.

Results: The vital signs were recorded for a cohort of 177 patients. There were twice as many males as female with no significant difference in age or average transport time (~25 minutes). Eight patients expired; mortality was due to multiple injuries (cerebral hemorrhage, cardiac arrest, abdominal injury, and chest injuries). ROC analysis of mean SPO2 VSDR vs. mortality produced an AUC of 0.76 (P=0.05) compared to 0.59 from the intermittent value of SPO2 TR (figure1). In a random pair of patients, VSDR correctly identified the deceased patient 76% of the time vs. 59% using the TR values. Analysis at 5, 10, and 15 minutes duration of mean SPO2 VSDR yielded AUC values ranging from 0.85 to 0.87 ($p<0.05$). SPO2 mean < 90% in the VSDR group had the highest predictive value producing an AUC of 0.73 ($p=0.0128$).

Conclusions: Continuously recorded mean SPO2 predicted mortality better than SPO2 values from TR. Clinical cut-off values for SPO2 VSDR still predict mortality significantly better than the trauma registry. Using mean SPO2 values from continuously recorded vital signs during pre-hospital transport can improve triage and reduce the 20-60% triage error rate and cost of inappropriate trauma care.[5]

Failure to Achieve Normothermia is Not Associated with Worsened Outcomes in Brain Injury Patients

Hyperthermia is a common finding in patients with traumatic brain injury (TBI) and may worsen patient outcomes. Many TBI management protocols use antipyretics and active cooling as a component of therapy even though it is often ineffective in maintaining normothermia. To investigate the predictive relationship between temperature, intracranial pressure (ICP), and neurological outcomes in the setting of a standardized therapy for hyperthermia, we analyzed continuously collected patient vital signs data and compared them to mortality, Extended Glasgow Outcome Scores at 3- and 6-months (3GOSE & 6GOSE), intensive care unit length of stay (ICU-LOS), and discharge Glasgow Coma Score (GCS) for patients with moderate-to-severe TBI.

Methods: Following IRB approval, continuous vital signs records were analyzed and compared to the following outcomes in 26 patients with TBI: mortality, 3GOSE > 4, 6GOSE > 4, ICU-LOS > 7 days, and discharge GCS > 8. Body temperatures were captured and plotted against concurrent temperature and divided into six sections (S1-S6) based on breakpoints of temperature (< 36, 36-38.5, or > 38.5 ^{o}C) and ICP (< 20 or ≥20 mm Hg) (Figure 1). Measurements of ICP and temperature were averaged over 5 mins. The percentage of "good monitoring time" (both temperature and ICP data available) spent in each section was evaluated for predictive by examining the area under the receiver operating characteristic curve (AUC) for several pooled conditions including: all potentially unfavorable combinations (S1-4,S6), hypothermia (S1,S4), hypothermia (S3,S6) and elevated ICP (S1-3).

Results: A total of 26 patients were evaluated in this study with a total of 111 days (32,0006 data points) of available data collection. Using the AUC, time spent in an unfavorable relationship respective to the normothermia/ICP < 20 mm Hg state (S1-4,S6) was a significant predictor of mortality and worsened 3MGOSE (Table 1). Hyperthermia with or without ICP elevation (S3,S6) was not predictive of a worsened outcome.

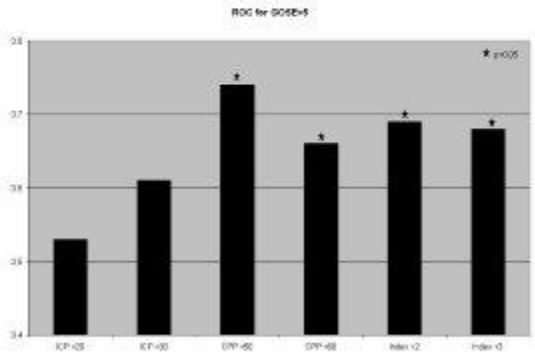
Summary: Hypo- and hyper-thermia were not predictive of worsened outcomes in the TBI patient using continuously derived vital sign data. Time spent outside of normothermia with/without elevated ICP is associated with higher mortality and worsened 3GOSE.

Brief Episodes of Intracranial Hypertension and Cerebral Hypoperfusion are Associated with Poor Functional Outcome Following Severe Traumatic Brain Injury

Objectives: Secondary insults following severe traumatic brain injury (sTBI) are known to be associated with poor outcome. The purpose of this study was to determine whether brief episodes of intracranial hypertension (ICH) and cerebral hypoperfusion (CH) worsen functional outcome after sTBI.

Methods: Patients with head AIS≥3, age>14, "isolated" TBI and need for intracranial pressure (ICP) monitoring were prospectively enrolled at a single large urban tertiary care facility. Outcome was measured by Extended Glasgow Outcome Scale (GOSE) at 6 months. Continuous, automated, digital data was collected every 6 seconds and 5 minute means were calculated for the duration of monitoring. Episodes of moderate (ICP>20) and severe (ICP>30) ICH and CH (CPP<50 and <60) were captured. Episodes of combined insults, measured by the Brain Trauma Index (BTI=CPP/ICP), were also recorded. The number of brief episodes per day were compared in the group with good functional outcome (GOSE>4) to those with poor outcome at 6 months. ROC curves were also calculated for prediction of poor outcome.

Results: 60 patients were enrolled. Demographics included: mean age 34 years (range 16-83), mean admission GCS 6.4 ±3.1, mean head AIS 4.2 ±0.7 and mean Marshall score 2.5 ±0.9. The 30-day mortality was 13%. 35 patients had good neurological outcomes (GOSE>4). The mean number of 5-minute episodes per day of ICP>30, CPP<50, CPP<60, BTI<2, and BTI<3 were greater in patients with poor functional outcome.



Conclusion: Episodes as brief as 5 minutes of severe ICH, moderate and severe CH, and the combination of these insults, as measured by BTI, are associated with poor outcome in patients with sTBI. Management of these patients should target prevention of these episodes and aggressive treatment once they occur.

Using Vital Signs Network to Improve Patient Safety: How Many Alarms are too many?

A hospital-wide biomedical engineering network was interfaced with a physiological data repository system with cross-references to clinical and outcome registry. We developed a method to mine the data for alarm events to understand the types and associated frequencies of alarms in a trauma resuscitation unit. Alarms were frequent (74 times per bed per day) with short durations (median: 4 sec). The vital signs network was useful to identify potential strategies to reduce clinical spurious alarms.

Introduction: Networked patient monitors provide continuous data that can be mined to examine factors impacting patient safety. High-frequency physiological data is captured, but methods to derive useful information are needed. We reported a way to use the monitor network to quantify clinical alarms into different categories useful to inform design of optimal alarm management practices. Methods: In a major trauma center, the 12 bed trauma resuscitation unit (TRU) received 7,800 patients last year. During a consecutive 4 week (28 day) period, the status of all patient TRU vital signs monitor alarms was recorded using the Excel Medical BedMasterEX software from the networked GE Solar patient monitors. Based on the nature of the alarm, we grouped the alarms into four categories: Patient Crisis, Patient Warning, Patient Advisory, and System Warning. Average admission Glasgow-Coma-Scale (GCS) was used to indicate criticality status of patients and duration of stay per trauma bay were determined from the trauma registry. The association of alarm frequency with patient admission status was assessed.

Results: Total of 24,787 alarms were recorded during the 4 week study period for all 12 beds. Among the alarms [Table 1], 258 [10.4 %] were for Patient Crisis,7,552 [30.4%] for Patient Warning, 6,496 [26.2%] for Patient Advisory, 10,481 [42.3%] for System Warning. Everyday an average of 74 [29-110] alarms were triggered per TRU bed. In the 4 weeks, 664 patients were admitted with an average of 37 alarms per patient: The top three (25%) TRU beds with most critical patients (based on average admission GCS) had 30% more alarms (44 alarms / patient) than the three (25%) TRU beds with the least critical patients (34 alarms / patient) with similar duration of stay. Median alarm duration and inter-quarter interval were 4 [2-16] sec. 55.1% and 69.1% of total alarms were less than 5 second and 10 seconds respectively. Top three reasons for alarms are SPO2 Probe (23.4%), Tachy (6.1%) and Leads Fail (6.1%).

Conclusion: By combining data from networked high frequency physiological monitors and clinical data from the trauma registry, we quantified problems of excessive short duration alarms 15.8/37.3 (42%) of were system, not patient related, making managing and using clinical monitoring alarms challenging. The median duration of alarms was 4 seconds, suggesting that the majority of the alarms were transient in nature. Patient safety may be improved by refining alarm management practices, such as using technology to filter out spurious alarms and improving system technology to minimize sensor disconnects. Our study suggests that a straightforward method that could avoid 65% of Patient Advisory and 51% System Warning alarms would be to introduce a 5-second delay.

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Traditional Systolic Blood Pressure Targets Underestimate Hypotension-Induced Secondary Brain Injury

Vital signs, particularly blood pressure, are often manipulated to maximize perfusion and optimize recovery from severe traumatic brain injury (sTBI). We investigated the utility of automated continuously recorded vital signs to predict outcomes following sTBI.

60 patients with head AIS≥3, age>14, "isolated" TBI and need for intracranial pressure (ICP) monitoring were prospectively enrolled at a single large urban tertiary care facility. Outcome was measured by mortality and Extended Glasgow Outcome Scale (GOSE) at 12 months. Continuous, automated, digital data was collected every 6 seconds for 72 hours after admission, and five minute means of systolic blood pressure (SBP) were recorded. We calculated SBP as pressure-times-time dose (PTD) to describe the cumulative amplitude and duration of episodes above and below clinical thresholds. The extent and duration of the insults were calculated as percent time (%time), PTD, and PTD per day (PTD/D) of defined thresholds (SBP<90, <100, <110 and <120, MAP<60 and <70, HR>100 and >120, SpO2 <88 and <92) for the first 12, 24, and 48 hours of ICU admission. We analyzed their ability to predict mortality and GOSE by receiver operator characteristics (ROC).

Mean age was 33.8 years (range 16-83), mean admission was GCS 6.4 ± 3, and mean head AIS 4.2 ± 0.72. The 30-day mortality rate was 13.3%. Of the 45 patients in whom GOSE at 12 months was available, 28 (62%) had good neurological outcomes (GOSE >4). Traditional markers of poor outcome (admission SBP, admission GCS, Marshall score) were no different between groups with good or poor outcome. PTD, PTD/D, and %time SBP<110 and SBP<120 predicted mortality at 12, 24, and 48 hours ($p<0.04$). Percent time SBP<110 in the first 24hrs was predictive of 12month GOSE ($p=0.02$). PTD/D SBP<120 in the first 24hrs, and PTD and PTD/D in the first 48hrs were also predictive of 12month GOSE ($p<0.05$).

Within the first 48 hours of ICU admission, hypotension was found to be predictive of mortality and functional outcomes at higher thresholds than traditionally defined. Systemic blood pressure targets closer to 120 mmHg may be more efficacious in minimizing secondary insults, and particularly useful in settings without invasive intracranial monitoring capabilities.

Pre-hospital Hypoxemia and Tachycardia Trends Better Predict Patient Mortality than Trauma Registry Values

Introduction

Early prediction of mortality in the field is challenging for patients with traumatic injuries. Currently triage and treatment algorithms depend on single 'snapshot' pre-hospital vital signs (VS) during transport. Modern monitors have the capacity to provide VS trends over time. We hypothesized that continuously recorded heart rate (HR) and pulse oximetry (SpO2) "Dose" (duration clinically abnormal values x frequency) can identify which trends predict mortality best in comparison to single values from the trauma registry (TR).

Methods

177 Trauma patient vital signs were automatically collected every second during the field transport via helicopter The first 5,10,15 min Dose of HR >100, >110, >120 beats/minute (bpm) and SPO2 <95%,<90% were calculated. The Doses (Dose-HR, Dose-SpO2) and the signal value from trauma registry (TR-HR, TR-SpO2) were analyzed to compare their ability to predict mortality by Receiver Operator Characteristic method. $P < 0.05$ was considered statistically significant.

Results

The average trauma patient helicopter transport duration was 25 mins. Patient mortality was 8/117 = 7%. The prediction power measured by Area Under the Curve (AUC) for Dose-HR (0.733-0.824, $p<0.0002$-0.018) and Dose-SpO2 (0.766-0.847, $p<0.0001$-0.005) were consistently better than TR-HR (0.60, $p<0.19$) and TR-SpO2 (0.591, $p<0.20$). Dose-HR>110 bpm and Dose-SpO2 <90% at 15 min was a better predictor of mortality than Dose-HR>120 bpm and Dose-SpO2 <95% at 5,10.15 mins (Table 1).

Conclusions

The dose of continuously recorded HR<110 bpm and SpO2 < 90% recorded every second show a significantly higher mortality predictive power than dose HR>120 bpm and SpO2 < 95% and single TR values during transport. Pre- hospital care and modern Registries would benefit from continuous trending by showing that SpO2 Dose < 90% and HR >110/min is a cause for concern because it predicts patient instability, mortality and the need for early trauma center intervention.

Support by W81XWH-05-0374, W81XWH-06-C-0034, and W81XWH-07-2-0118

Brief Episodes of Abnormal Shock Index Predicts Mortality in Severe Traumatic Brain Injury.

Introduction: Shock index (SI = heart rate (HR/ systolic blood pressure (SBP)) has been used to predict pre-hospital mortality in trauma patients. We examined brief episodes of abnormal Shock Index (SI> 0.7) as an early predictor of mortality and length of stay in intensive care (ICU) of severe traumatic brain injury (TBI) patients.

Methods: continuous, automated, digital vital signs (VS) data were recorded every 6 seconds on ICU patients with severe, isolated TBI. We then calculated five-minute means of SI (HR/SBP) and the number of episodes (5 to 60 minutes in increments of 5 minutes) above-normal SI (SI 0.7 to 1.0 in increments of 0.05) at intervals over the ICU stay. We then used Receiver Operatory Characteristic (ROC) methods to determine the predictive power of these episodes for 30-day mortality and length of ICU stay over 14 days (LOS).

Results: Twenty-one patients provided 6,200 hours of VS data (3,720,000 data points). Area Under the Curve (AUC) for the predictive power of episodes of above-normal SI for mortality ranged from 0.52 to 0.87 and for LOS, 0.58 to 0.95. SI >0.7 lasting > 10 minutes best predicted mortality (AUC 0.84, -<0.0001) in the first 12 hours of ICU admission. SI >0.7 lasting >25 minutes best predicted LOS (AUC 0.87, p<0.001) at 48 hours. With all ICU VS included, SI >0.7 lasting >15 min provide the best prediction of mortality (AUC 0.85, p< 0.0001) and LOS (AUC 0l95, p<0.0001).

Conclusions: SI calculated from continuous automated VS recordings predicts mortality and LOS as early as the first 12 hours of ICU stay. We are now deploying and validating a real-time telemetric VS viewer that includes SI with other continuous VS displays from our tertiary care trauma center Neurotrauma ICU.

Real-Time Decision Support During Trauma Patient Resuscitation

Optimal management of shock during the initial resuscitation of patients with major trauma may have salutary effects on their subsequent hospital course (1). Computer assisted decision making during resuscitation has been shown to decrease morbidity (2). We describe a prototype automated continuous vital signs data collection and decision support system and illustrate the potential real-time applications during trauma patient resuscitation.

Methods: After Institutional Review Board approval, data was collected and stored on a vital signs data recorder (VSDR), from trauma patients admitted to University of Maryland Shock Trauma Center (STC). Continuously recorded vital signs waveform and interval data were captured of electrocardiogram (ECG), oxygen saturation (SPO2 %), end-tidal carbon dioxide, and non-invasive and invasive blood pressure from all GE patient monitor devices throughout the patient care areas. Waveforms were input into a software application created in Mathlab (www.mathworks.com). Real-time signal processing, plotting and analysis used MedCalc (www.medcalcsoftware.com). Abnormal physiological data (outside pre-defined threshold limits from published anesthesiology, surgery and critical care algorithms) were automatically highlighted in green yellow or red indicating severity of deviation from normality. Composite signals, such as Shock Index, Brain Trauma Index (3) were calculated and their cumulative 'dose' calculated. Data displays were connected to the STC intranet to allow remote viewing.

Results: The automated collection and real-time composite analysis of continuous waveforms from vital signs provided predictive trends of bleeding (see Fig 1 showing Shock and Brain Trauma Index (BTI)) and identified actionable interventions, including need for increased oxygenation, reduction of intra-cranial pressure, hemorrhagic shock resuscitation, blood transfusion (with additional oximetry analysis), with a user-friendly intuitive interface. Individual patient data can be retrieved and displayed on any time frame from seconds to days. Real-time decision support data from multiple patients (up to 24) can be displayed simultaneously at co-located or remote locations.

Discussion: Unstable patients were able to be rapidly identified during resuscitation. Needed interventions could be identified by co-located or remote viewing. Combinations of vital signs data (Shock Index and BTI) were robust in predicting outcomes and assessing impact of interventions (3). In clinical trials real-time decision support significantly increased error-free resuscitations during the first 30 minutes of resuscitation when a critical decision was made every 72 sec (1,2). Reports of critical events depend on recall by the participants at a later date, often months or years after the incident. Using VSDR with continuous data collection, what happens in life-threatening emergencies during resuscitation is no longer anecdotal. Our approach using analysis of continuous patient vital signs waveforms adds no additional equipment and can be incorporated as a software upgrade to central monitoring systems or individual patient monitors. A prospective trial is needed to assess error reduction, morbidity and mortality outcome with real-time vital signs decision support.

1)Arch Surg 2011; 146: 225, 2) Arch Surg 2011; 146: 218, 3) J Trauma 2010; 69: 11

Use of Serum Biomarkers to Predict Cerebral Hypoperfusion following Severe Traumatic Brain Injury

Purpose:
The management of severe traumatic brain injury (sTBI) focuses on prevention and treatment of secondary insults, such as cerebral hypoxia (CH). Predicting which patients will develop these secondary insults is currently not possible. This study evaluates the association between serum biomarkers and CH as measured by brain tissue oxygen partial pressure (Pb02) in patients with sTBI.

Methods:
Patients with sTBI (head AIS>3, age>14, "isolated" TBI, need for intracranial pressure monitor) were prospectively enrolled. Serum was collected within 24 hours of injury and twice daily for 7 days. Pressure times time (PTD; mmHg*h), measuring the depth and duration of CH, was calculated for 12-hour periods for episodes of moderate and severe CH (PbO2<20 and <15mmHg) and compared to serum levels of neuron-specific enolase (NSE), S100-beta (S100b), and glial fibrillary acidic protein (GFAP) drawn prior to periods of monitoring. Specimens were analyzed by ELISA. Adjusted mixed models accounted for longitudinal correlations within patients and analysis was conducted of area under the curve (AUC) obtained from Receiver Operating Characteristics (ROC) curves.

Results:
Of 68 patients enrolled, 24 had PbO2 monitoring. 130 serum samples were matched with 12-hour periods of monitoring. Significant correlations were found in adjusted analysis between serum levels of NSE, S100b, and GFAP and PTD of moderate ($p<0.01$) and severe ($p<0.01$) CH. AUCs for classification of moderate and severe CH ranged from 0.55-0.71 for NSE and S100-b, indicating fair to good accuracy, with specificities between 76 and 90%.

Conclusions:
NSE, S100-b, and GFAP demonstrate promise as candidate serum markers of impending CH. These data suggest that we may be able to ‘predict' imminent events following TBI prior to clinical manifestations. Given the morbidity of CH, early intervention and prevention may have a significant impact on outcome and help guide decisions about timing of interventions.

Summary of Staff, Roles and Percent Effort by Project/Sub-project

STAFF MEMBER	ROLE	% EFFORT (%FTE)
Thomas Scalea	PI	1.6
Lisa Gettings	Administrator	0
Karen Murdock	Project Manager	5
Colin Mackenzie	Sub-Project PI; Vital Signs study	donated
Peter Hu	Co-Investigator	11.1
Yan Xiao (resigned)	Technical Support	0
Steven Seebode (resigned 10/6/10)	Technical Support	0
George Hagegeorge (hired 2/28/11)	Technical Support	15
Jessica Baroody	Technical Support	100
Shiming Yang	Student Assistant	0
Eric Lund	IT Application Engineer	50
Deborah Stein	Sub-project PI; Cytokine study	2.9
Kevin Sheth	Sub-project Co-PI	2.5
Bizhan Aarabi	Co-Investigator	1
Richard Dutton	Co-Investigator	0
Allison Lindell (resigned 7/30/11/0	Coordinator; Cytokines study	0
Kaspar Keledjian	Cytokine technician	0
Robert Rosenthal	Sub-project PI; Animal model	1.07
Gary Fiskum	Co-Investigator	8.3
Karen Volpini	Database Management	0
Madeline Mitrou (resigned 1/1/11)	Research Nurse	0
Yawei Wang	Research Nurse	52.5
Amechi Anozado	Research Assistant	0
Margaret Mensa	Research Nurse	41.9
Diane Rouse (resigned)	Research Nurse	0
Marianne Hattan	Research Nurse	89.1
Bonnie McManus (resigned 6/23/11)	Research Nurse	0
Keri Volpini	Research Assistant	18.3
Christine Wade-Mariani	Research Assistant	3
Charles Simpson (resigned)	Research Assistant	0
Scott Berry (resigned)	Research Assistant	0
Tondeleyo Gonzalez	Research Assistant	2.3
Carrie Sauer (resigned)	Research Assistant	0
Olga Kolesnik	Research Assistant	60
Sean Jordan (resigned)	Research Assistant	0
Sara Wade	Research Assistant	37.4
David Prakash (resigned 12/31/10)	Research Assistant	0

Ryan Gens (resigned)	Research Assistant	0
Cris Imle	Physical Therapist	0
Myra Collins (resigned 7/13/10)	Research Assistant	0
Jonathan Gooch	Research Assistant	8.1
Sean Crane	Research Assistant	0
Daniel Mayer	Research Assistant	3.3
Jamila Torain (hired 2/15/11)	Research Assistant	5
Emily Cooper (hired 1/18/11)	Research Assistant	15.6
Genna McFarland (resigned)	Student Assistant	0
Kristina Clem (resigned)	Data Entry	0
Joe Kufera	Statistician	5
Gordon Smith	Epidemiologist	0
Julie Hazleton	Technician	25
Jennifer Racz (resigned)	Technician	0
Xiaoli Xiao (resigned)	GRA	0
Wei Xiong (resigned 12/31/10)	GRA	0
Keng-Hao Liu	GRA	0
Tiffany Greco	GRA	0
Yu Wei Chang (resigned)	Data Processor	0
Ryan Seebode	Data Entry Assistant	100
Susanna Scafidi	Co-Investigator	0
Matthew Woodford (resigned 12/15/10)	Post-doctoral Fellow	0
Irina Balan	Post-doctoral Fellow	75
Rao Gulliapalli	Co-Investigator	0
Matt Lissauer	Co-Investigator	1.0
Jiachen Zhuo	Post-doctoral Fellow	0
Josh Ayres	Student Assistant	0
Lynn Stansbury	Medical Editor	10

* 100% effort for a GRA is 20 hours/week